The National Cancer Institute's Clinical Trials Cooperative Group Program:
An Infrastructure in Transition
BACKGROUNDER

Summary:
For over 50 years, the National Cancer Institute NCI has supported a standing infrastructure - the NCI Clinical Trials Cooperative Group Program - to conduct large-scale cancer clinical trials across the nation, with successful completion of many important trials that have led to new treatments for cancer patients. Over time, however, oncology has evolved into a more molecularly-based discipline including genetic sub-classification of tumors and individualized treatments. It is truly an exciting time in oncology research, and we are presented with immense scientific opportunities to be systematically explored. NCI must ensure that the Cooperative Groups are optimally situated and well-prepared to design, enroll, and complete state-of-the-art trials for cancer patients.

The Institute of Medicine (IOM) of the National Academies was asked by the National Cancer Institute (NCI) to review the Institute's Clinical Trials Cooperative Group Program; to gather independent, expert perspectives on the state of cancer clinical trials in the United States; and to provide advice about ways to improve the NCI Cooperative Group Program. The IOM report, "*A National Cancer Clinical Trials System for the 21st Century: Reinvigorating the NCI Cooperative Group Program*," was issued in April 2010. While the report recognizes that "publicly funded clinical trials play a vital role by addressing questions that are important to patients but are less likely to be top priorities of industry…," it goes on to recommend that the Program be restructured and its funding increased. The report states that the "Program is falling short of its full potential to improve the quality of care that cancer patients receive" and notes that many of these shortcomings are due to inefficient, cumbersome, underfunded, and overly complex systems. The IOM report viewed favorably the changes that NCI has implemented to the Cooperative Groups in recent years, including the Cancer Trials Support Unit (CTSU), the Central Institutional Review Board (CIRB), and disease-specific steering committees. However, the report found that the system requires a major transformation that can only be accomplished by consolidating the existing adult groups into a smaller number of groups that can function in a more closely integrated manner.

Background: What is the NCI Clinical Trials Cooperative Group Program?

Founded over 50 years ago, the NCI Clinical Trials Cooperative Group Program is composed primarily of 10 U.S.-based groups that involve more than 3,100 institutions and 14,000 investigators, and that enrolls more than 25,000 patients in clinical trials each year. The program is noted for its involvement of physicians and patients from diverse communities who help ensure that the results of clinical trials are meaningful to a broad segment of the U.S. population. Over the past 50 years, over 17 Cooperative Group trials have significantly affected how oncology is practiced currently in the United States. The

clinical trials conducted by the Cooperative Groups also provide a valuable mechanism for the training of clinical investigators. A list of the 10 U.S.-based NCI Cooperative Groups can be found at http://www.cancer.gov/cancertopics/factsheet/NCI/clinical-trials-cooperative-group

What Changes Have Already Taken Place?

While the IOM review was underway during the past year, NCI was already implementing many ideas that were ultimately recommended in the final IOM report. For example:

- **Increasing reimbursement to sites:** NCI has recently increased the per case reimbursement rates from $2,000 to $5,000 per enrolled patient *for phase 2 studies*, and added additional funding beyond the standard $2,000 per patient for *selected phase 3 trials* based on their complexity.
- **Setting deadlines for trial development:** Studies have shown that a trial that does not open to accrual within 2 years of concept submission is very unlikely to reach full accrual. After that length of time, the scientific questions have often evolved, and there are typically more scientifically relevant studies being proposed. Based on this analysis, NCI instituted new deadlines, which will take effect January 1, 2011, enacting the recommendations of the Operational Efficiency Working Group (OEWG)[1] to cut in half the time it takes to initiate new clinical studies and to terminate studies not activated within 2 years of concept approval. As of April 15, 2010, all new studies are undergoing a revised approval and implementation process which target going from the initial idea to study concept activation within 7 and 10 months respectively for phase 2 and 3 trials.
- **Funding dedicated staff positions for rapid trial development:** To aid the more rapid implementation of trials, the American Recovery and Reinvestment Act of 2009 (ARRA) provided the opportunity for NCI to fund dedicated staff positions, both within NCI and at the Cooperative Groups, with key expertise such as science writing and clinical trials management to keep trials on schedule. The goals of this funding are: (1) to ensure that trial development steps occur in parallel; (2) to facilitate timely, coordinated interactions to resolve issues related to protocol review; and (3) to ensure continuous use of protocol tracking tools and overall project management.
- **Prioritizing the most important trials:** NCI has revamped the process for prioritizing large phase 2 and 3 cancer treatment and control trials. In place of the previous NCI-only review, the Institute has established disease-specific and modality-specific (imaging and cancer control)

[1] The NCI Clinical Trials and Translational Research Advisory Committee (CTAC) established the Operational Efficiency Working Group to recommend strategies for reducing the time for activation of Cooperative Group and Cancer Center trials. The 68-member group includes leadership from the Cooperative Groups, Cancer Centers and community oncologists, as well as representatives from the FDA, CMS, and NCI.

steering committees comprised of expert investigators from the Cooperative Groups and Cancer Centers, along with patient advocates, to prioritize the best ideas for these large-scale trials. Once the trial ideas are approved by these steering committees, NCI staff works with the lead investigators to facilitate rapid development of the final study, coordinating with other key stakeholders such as pharmaceutical collaborators and the Food and Drug Administration (FDA) as necessary.

- **Encouraging common business practices across cooperative groups:** NCI has already achieved a good deal of integration by forming the CTSU - a program started around 2000 but greatly expanded over time and continually being improved - that provides the Cooperative Groups' operations offices, the investigator sites and patients with a one-stop shop for protocol-related materials and information. The CTSU provides a single repository for all regulatory documents across all Cooperative Group trials and it offers a 24-7 online registration system for all Cooperative Group trials. Most importantly, it allows investigators irrespective of their Cooperative Group membership to enroll their patients in any suitable trial on the CTSU menu. This has permitted over 40% of enrollments to Cooperative Group trials to come from sites that are not a member of the group leading the trial. NCI has invested in standardizing case report forms, defining data elements, and bringing uniform database capabilities of all the groups.
- **Modernized clinical trials IT infrastructure:** NCI is in the process of procuring a single information system (clinical trials data management system) for the entire NCI clinical research enterprise which will facilitate a series of innovations including:
    - Standardized case report forms
    - A common protocol authoring tool
    - Consistent audit standards
    - Enhanced data sharing
- **Improving efficiency and utilization of the NCI CIRB:** NCI has been working to increase utilization of the NCI CIRB, improving efficiency overall and decreasing the average time for final sign-off on a national protocol from 150 days in 2007, to 42 days in 2009-2010. NCI is also in the process of obtaining national accreditation for the CIRB, which should significantly increase its use. Approximately 700 cooperative group sites (out of 1800) already use the CIRB, and more than half of NCI's Comprehensive Cancer Centers are using it too.

Why Do the Groups Need To Be Consolidated?

The practice of oncology has evolved significantly with the development of molecular oncology, a new area of cancer research focused on the molecular and chemical basis of malignant transformation, including the assessment of specific processes related to cancer cells, genetic changes, and drug and hormonal response and resistance. This evolution in our understanding of cancer also requires an evolution in the design and implementation of clinical trials.

For example, modern clinical trials typically utilize sophisticated genetic profiling of tumors, and these types of studies necessitate the screening of large numbers of patients to find subsets of patients with tumors that demonstrate changes in specific genetic pathways. These types of trials require the development of systems for specimen acquisition and distribution, DNA sequencing of specimens, molecular stratification, and correlation with genomic data. This necessarily increases the complexity of these trials, and multi-disease, multi-modality groups with adequate resources are best suited for managing such complex trials. In addition, a few large Cooperative Groups will be better able to meet the needs for investigator training and for the clinical adoption of new discoveries.

Our current Cooperative Group structure - with several small groups - makes it difficult to complete clinical trials based on the stratification of molecular tumor characteristics. In the future, these smaller groups will be less competitive in light of the relatively small sizes of their infrastructures and staff. In view of the changing nature of clinical trials, some of the Cooperative Groups have already independently begun to consolidate their data management operations and are beginning to discuss integration of their scientific programs.

Consistent with the IOM recommendations, NCI has concluded that a smaller number of large Cooperative Groups with broad membership and the ability to function as a coordinated network will be better able to execute the complex clinical trials that the state of the science demands. Therefore, we are now discussing with our Cooperative Group leadership how to implement the consolidation called for by the IOM.

How Many Cooperative Groups Will There Be?

There are currently 10 U.S.-based Cooperative Groups - nine adult groups and one pediatric group. We are currently engaged with Cooperative Group leadership in developing an approach to implementing the IOM recommendation to consolidate to a maximum of four adult groups and one pediatric group. NCI expects that merging the existing nine adult groups into no more than four multi-disease adult groups will fulfill the need for complex, multidisciplinary cancer trials, achieve more sophisticated capabilities across the board, and facilitate highly integrated group structures. As discussions concerning how best to address the consolidation of the groups continue, the unique needs of sub-specialists (e.g. radiation therapy, surgery, imaging) and their unique capabilities in cancer prevention, screening and diagnosis must be considered. The four pediatric clinical trials groups were merged previously into one entity (the Children's Oncology Group), which NCI expects to remain in its current form.

The consolidation to fewer adult groups will reduce redundancy and improve the effectiveness and efficiency of trials. Consolidation will result in streamlined and better-harmonized operations centers, data

management centers and tumor banks. Fewer group disease committees should also foster a more collaborative approach to selecting the most important trials to perform.

How Will the Consolidation Affect Patients and Researchers?

NCI remains committed to completing all currently active Cooperative Group trials. Once the consolidation is completed, we anticipate that this improved nationwide system of efficient clinical trials will provide the most rapid and effective transfer of new treatments and cancer control discoveries to patients.

Consolidation of the adult groups is expected to permit competition for the best trial ideas yet encourage collaboration among researchers. In anticipation of potential investigator concerns about consolidation, NCI has identified several strategies that may ease the transition to fewer groups:

- Permit multiple principal investigators on a single trial, as is allowed by NIH grants
- Incentivize the transition with additional resources
- Allow ongoing trials to continue with a distributed data management and operations system until they are completed
- Combine (rather than disband) the various groups' overlapping disease committees to include all current participants

How Will the Cooperative Groups Be Evaluated?

Evaluations will focus on how well new clinical trials are developed and completed, and how well the components of the clinical research infrastructure are integrated and managed. The NCI and Cooperative Group leadership will manage the program as a collaborative national program to reach shared goals - not as separate "grants," but as components of an integrated system. The system will be managed and reviewed as both a scientific enterprise and an operational enterprise.

Do the Cooperative Groups Have Input Into NCI's Decisions On This Issue?

NCI has already begun the process of seeking the active input of the Cooperative Groups in the implementation of the IOM recommendations. In light of the complexity of the process of consolidation, a significant, mutually interactive effort by the groups and NCI will be required to develop an implementation process that will lead to substantive improvements in the clinical trials program as a whole. Furthermore, each of the current Cooperative Groups will need to determine how best to accomplish its individual scientific goals as part of an integrated NCI clinical trials system. We realize that a change of this magnitude will require dialogue and planning with multiple stakeholders, including Cooperative Group board members, physicians involved in the groups, the broader scientific community, and scientific societies, industry, patients, and patient advocates. Stakeholders will be given the opportunity to

comment on the proposed consolidation, and to explore specific aspects of the consolidation plans in discussions with NCI program leadership.

NCI is working with the Cooperative Groups and critical stakeholders, including current Cooperative Group principal investigators, professional groups, and patient advocates to develop consensus. Opportunities for presentations at Group meetings, one-on-one meetings, and feedback on the website will be provided.